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09/508,083	07/03/2000	WOLF GEORG FORSSMANN	P65123US0	8457

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/508,083	Applicant(s) FORSSMANN ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *38-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

The Election of the compound of Claim 38 in which R=H, with traverse in Paper No. 12 has been considered. The argument that the restriction is not proper because it would necessitate dividing a generic claim is not persuasive because the various compounds claimed are not so linked to form a general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical feature for the reasons provided in the previous Office Action. Moreover,

Status of the Claims

Claims 1-37 were cancelled and Claims 38-59 were added in the Supplemental Preliminary Amendment filed October 29, 2001 (Paper No. 9). Therefore, Claims 38-59 are pending and will be considered in this Office Action.

Specification

The Specification and Claims are objected to because they fail to comply with the sequence rules (see MPEP 2420-2422 and 37 CFR 1.821-1.825). The Specification should refer to the amino acid sequence on page 6 by providing the sequence in three-letter code and including a sequence identifier (SEQ ID NO:)(see especially 37CFR 1.821(d) and 37 CFR 1.822(d)). The same correction should be made to the sequence provided in Claim 38. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-55 and 57-59 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41-55 are indefinite as to the position of the amino acid substitution to be made. The claims refer to substitutions in the compound of Claim 38 wherein specific amino acid residues at particular positions are to be substituted. However, the amino acid residues recited do not appear in the recited positions in the compound of Claim 38. Thus, the claims are not clear as to whether the amino acids referred to therein are to be substituted or the amino acid position is to be substituted. The indefinite positioning is provided as follows:

Claim 41 refers to "the lysinee amino acid in position 26 and/or 34" however, positions 26 and 34 of the sequence provided in Claim 38 (from which Claim 41 depends) are not lysines.

Claim 42 refers to "tryptophan in position 31 is substituted" in reference to the sequence of Claim 38 which has only 28 amino acid positions. Clarification is required.

Claim 43 includes substitutions at Valine in position 16, Serine in position 18, Glycine in position 22, Glutamine in position 23, and lysine in position 26. However, these amino acid residues do not appear at the recited positions. It is noted that the

claim correctly refers to glutamate at position 21 and alanine at position 24. Clarification is required.

Claim 44 refers to substitutions of the compound of Claim 38 wherein the substitutions include Alanine in position 8, glutamate in position 9, glycine in position 10, and aspartate in position 15. However, these amino acid residues do not appear at the recited positions.

Claim 45 refers to alanine in position 8. The compound of Claim 38 does not appear to have an alanine at position 8.

Claims 46 and 51 refer to the histidine amino acid in position 7. The compound of Claim 38 does not appear to have a histidine at position 7.

Claim 47 refers to the lysine amino acids in positions 26 and/or 34. The compound of Claim 38 does not appear to have lysines at these positions.

Claim 48 refers to the tryptophan amino acid in position 31. The compound of Claim 38 is not 31 amino acids in length.

Claim 49 refers to positions glycine in position 22, glutamine in position 23, or a lysine in position 26. The compound of Claim 38 does not appear to have these amino acids in the positions given. It is noted that the compound of Claim 38 does have an alanine in position 24 and glutamate in position 21 as recited in Claim 49..

Claim 50 refers to the alanine of position 8, glutamic acid in position 9, and glycine in position 10. The compound of Claim 38 does not appear to have these amino acids in the positions given.

Claim 52-55 refers to the histidine in position 7 and the alanine in position 8. The compound of Claim 38 does not appear to have these amino acids in the positions given. Correction is required.

Claim 57 is indefinite because it refers to the "composition" of claim 38 but Claim 38 is drawn to a compound and not a composition. Correction is required. Claims 58 and 59 are also rejected since they depend from claim 57 yet do not correct its deficiencies.

Claim 57 is indefinite for the recitation of "for the treatment of secondary hyperglycaemias in connection with pancreatic diseases (chronic pancreatitis, pancreatectomy, haemochromatosis)" or endocrine diseases (acromegaly, Cushing's syndrome, phaeochromocytoma, or hyperthyreosis, for the treatment of hyperglycaemias induced by drugs (benzathiadiazine salidiuretics, diazoxide, or glucocorticoids)". The claim is unclear as to whether the diseases and drugs listed in the parentheses are intended only to be examples of the broad pancreatic and endocrine disease and drug categories named before the parenthesis (equivalent to "such as") or if the claim is limited to these specific diseases and/or drugs. Correction is required. (see MPEP 2173.05(d) if the parenthesis are equivalent to "such as"). Claims 58-59 are rejected since they depend from this indefinite base claim yet do not correct its deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical containing a compound according to claim 38 for the therapy of insulin-independent diabetes mellitus, does not reasonably provide enablement for pharmaceuticals containing the compound according to claim 38 for the therapy of insulin-dependent diabetes mellitus, MODY, secondary hyperglycaemias in connection with pancreatic diseases (chronic pancreatitis, pancreatectomy, haemochromatosis), endocrine diseases (acromegaly, Cushing's syndrome, phaeochromocytoma, or hyperthyreosis, hyperglycaemias induced by drugs (benzathiadiazine salidiuretics, diazoxide, or glucocorticoids), pathologic glucose tolerance, hyperglycaemias, dyslipoproteinaemias, obesity, hyperlipoproteinaemias, and/or hypotonias. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It would require undue experimentation for one of skill in the art to practice the claimed invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention involves the discovery that GLP-1 (7-34)(peptide of Claim 38) has a longer half-life than that of GLP-1 (7-36) amide and that infusion of GLP-1 (7-34)COOH and GLP-1(7-34)Amide in equimolar amounts results in higher insulin release and higher reduction of glucose levels than GLP-1(7-36) Amide does (see p. 2-3 of present Specification).

The Claims broadly encompass the intended use of claimed peptides having the sequence of GLP-1(7-34) and peptides with modifications in that sequence in the treatment of a wide variety of diseases of various tissues, wherein each disease involves unique mechanism and unique set of involved factors and problems.

The state of the prior art and the relative skill in the prior art is such that the peptide of present Claim 38 is well known in the prior art and has been suggested for use in the treatment of insulin-independent diabetes mellitus (non-insulin dependent or type II diabetes) (see prior art references below). However, there appears to be no teaching or suggestion of using peptides similar or identical to that of Claim 38 in the treatment of the additional diseases listed in present Claim 57-59. While the level of relative skill in the art is high, one of skill in the art would require some guidance as to how the peptide is related to each disease state, how much of the peptide to administer, and what mode of administration to obtain any expectation of success in treatment. Drucker (Endocrinol. (2001) 142(2): 521-527) indicates that even for the treatment of diabetes, further evaluation/experimentation of the efficacy of GLP-1 in treating diabetes is necessary including further research on how the protein can be administered (see p. 525, Col. 1, last paragraph).

The only guidance provided in the Specification is a mere mention that the peptides of the invention could be used in the treatment of the various diseases (p. 10). The Specification also suggests some dosages but does not specify what diseases or conditions those dosages could be used to successfully treat (p. 13).

There are no working examples in the present Specification.

In light of the factors described above (no teaching or understanding of how GLP-1 is related to the wide variety of disease claimed; recognition in the art that, even in the case of treating diabetes, further research is necessary to determine what modes and dosages of GLP-1 could possibly be effective in treatment; lack of any teaching, in the Specification or prior art, of forms of administration or dosages for any specific disease) it appears that it would be highly unpredictable whether or not the GLP-1 proteins claimed would be effective to treat the wide variety of diseases claimed. Moreover, what administration mode and dosage would allow successful treatment of any given disease would also be highly unpredictable.

Therefore, undue experimentation would be required to characterize the involvement of the claimed GLP-1 proteins in each specific disease and determine what form of administration and what dosage would be effective to treat each specific disease. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of the role (if any) played by the GLP-1 protein in each disease state and then the determination of how the protein can be effectively

administered to treat each disease. It is this additional characterization of the protein, its relationship to disease, and effective administration forms that is required in order to make and use the claimed proteins for their intended use that constitutes undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Buckley et al. (WO 91/11457, 1991; ref. AD in IDS of Paper No. 7).

Buckley et al. disclose a GLP-1 peptide, referred to as GLP-1 (7-34) that has general formula identical to present Claim 38 and teach and claim making modifications to the disclosed peptide that are identical to present Claims 41-55.

For example, the substitutions of Claim 41 are taught on page 5, lines 3-5 and in claim 1(a) of Buckley et al. The substitutions of Claim 42 are taught on p. 5, lines 7-8 (part (b)) and in claim 1(b) of Buckley et al. The substitutions of Claim 43 are taught on p. 5, lines 9-16 (part (c)) and in claim 1(c) of Buckley et al. The substitutions of Claim 44 are taught on p. 5, lines 17-25 (part (d)) and in claim 1(d) of Buckley et al. The substitutions of Claim 46 are taught on p. 5, lines 26-28 (part (e)) and claim 1(e) of Buckley et al. The substitutions of Claim 47 are taught on page 35, claim 2 of Buckley

et al. The substitutions of Claim 48 are taught on page 35, claim 3 of Buckley et al. The substitutions of Claim 49 are taught on page 35, claim 4 of Buckley et al. The substitutions of Claim 50 are taught on page 36, claim 5 of Buckley et al. The substitutions of Claim 51 are taught on page 36, claim 6 of Buckley et al. The limitations of Claim 52 are met on page 37, claim 8 of Buckley et al. The substitutions of Claim 53 are taught on page 38, claim 9 of Buckley et al. The substitutions of Claim 54 are taught on page 38, claim 10 of Buckely et al. The substitutions of Claim 55 are taught on page 38, claim 11 of Buckley et al.

Buckley et al. teach that these modified forms of GLP-1 (7-34) show a more potent effect on insulin release from isolated rat islets in culture, or by enhanced stability in plasma or both (p. 7, lines 22-27). Buckley et al. also teach using the modified GLP-1(7-34) compounds in methods of treating diabetes (see Buckley et al. clms 12-13).

It is noted that Buckley et al. only teach modified forms of the compound of the present invention and do not teach or suggest using the compound having the formula of Claim 38 without the modifications taught in Buckley. Thus, present Claim 38 does not appear to be anticipated by Buckley et al.

For the reasons provided above, it appears that Buckley et al. meet the limitations of Claims 41-55.

Claims 38-40 and 56-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Danley et al. (EP 0 619 322, 1994).

Danley et al. meets the limitations of the claims because Danley et al. disclose a compound having identical general formula to that of the compound of present Claim 38 (see sequence alignment attached to this Office Action, SEQ ID NO: 5 of Danley et al., and p. 47, clms. 1 and 2, SEQ ID NOs: 5 and 7 of Danley et al.). Danley et al. discloses making carboxyamide derivatives of the disclosed peptides for peptide synthesis and thus meets the limitations of Claims 39-40 (see p. 17, lines 28-30). Danley et al. is considered to meet the limitations of Claims 57-59 because the compositions of Danley et al. contain the same compound and are therefore patentably indistinguishable from that of the present Claims 57-59. Danley et al. teaches that the compositions containing the compounds are for treatments of insulin-independent diabetes and are in a form by which release is attained in a long-lasting or pulsatile manner and wherein the form is suitable for subcutaneous, intravenous, peroral, intramuscular, or transpulmonary administration (see p. 60, clm. 14; p. 17, line 56; and p. 18, lines 4-5).

Claim 38 and 56-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Habener (US Patent No. 5,118,666, 1992).

Habener meets the limitations of Claim 1 because Habener discloses a compound having identical general formula to that of the compound of Claim 38 (see sequence alignment attached to this Office Action and clm.1A of Habener).

Habener meets the limitations of Claims 57-59 since Habener teaches a composition containing a compound identical to that of present Claim 38. The Habener

composition and the composition of the present invention appear to be patentably indistinguishable since both contain the same components.

Thus, Claims 38 and 57-59 appear to be anticipated by Habener.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
August 8, 2002

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